

Tea drinking and the risk of biliary tract cancers and biliary stones: A population-based case-control study in Shanghai, China

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Biliary tract cancers, encompassing tumors of the gallbladder, extrahepatic bile ducts and ampulla of Vater, are rare but highly fatal malignancies. Apart from gallstones, etiologic factors for biliary tract cancer are not clearly defined. Several epidemiologic studies have suggested that consumption of tea, especially green tea, is protective against a variety of cancers, including gastrointestinal malignancies. As part of a large population-based case-control study of biliary tract disease in Shanghai, China, we evaluated the effects of tea consumption on the risk of biliary tract cancers and biliary stones. The study included 627 incident cases with biliary tract cancer, 1,037 cases with biliary stones and 959 randomly selected controls. Study subjects were interviewed to ascertain data on demographic, medical and dietary factors, including tea consumption. Forty-one percent of the controls were ever tea drinkers, defined as those who consumed at least 1 cup of tea per day for at least 6 months. After adjustment for age, education and body mass index, among women, ever tea drinkers had significantly reduced risks of biliary stones (OR = 0.73, 95% CI = 0.54–0.98) and gallbladder cancer (OR = 0.56, 95% CI = 0.38–0.83). The inverse relationship between tea consumption and gallbladder cancer risk was independent of gallstone disease. Among men, tea drinkers were more likely to be cigarette smokers, and the risk estimates were generally below 1.0, but were not statistically significant. Further studies are needed to confirm these results in other populations and clarify the hormonal and other mechanisms that may be involved.

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Key words: biliary tract cancers; gallstones; tea consumption; polyphenol; epidemiology

Biliary tract cancers, consisting of tumors of the gallbladder, extrahepatic bile ducts and ampulla of Vater, are rapidly fatal.^{1,2} Although these cancers are uncommon in most parts of the world, incidence rates are elevated among native Americans and Hispanics living in the United States and among populations in Central and South America, Eastern Europe and Japan.^{1,2} Because of the rarity and high fatality of biliary tract cancers, little is known about their etiology apart from a strong link with gallstones.²

A number of epidemiologic studies have suggested that consumption of tea, especially green tea, is protective against certain cancers, including tumors of the lung, stomach, pancreas and esophagus.^{3–6} The antitumor effects of green tea have been attributed to polyphenols, which in laboratory studies have demonstrated inhibitory effects on tumor growth.^{7–10} Results of epidemiologic studies examining the association between tea consumption and biliary tract cancer have been mixed, perhaps due to the small number of cases, different types of tea consumed and lack of data on potential confounding factors, such as gallstone disease, diet and cigarette smoking.^{11–14}

In this report, we evaluate the effect of tea consumption on the risk of biliary tract cancers and biliary stones as part of a large population-based case-control study conducted in Shanghai,

China, where the incidence rates for these cancers have risen sharply in recent years.^{1,15}

Material and methods

Study subjects

Details of the study methods have been reported elsewhere.^{16–18} Briefly, cancer cases were permanent residents of urban Shanghai, between 35 and 74 years of age, who were newly diagnosed with biliary tract cancer (ICD9 code 156) between June 1997 and May 2001. The rapid reporting system established in 42 collaborating hospitals in Shanghai captured more than 95% of the incident cases diagnosed during the study period. A total of 627 cancer cases, including 368 gallbladder, 191 extrahepatic bile duct and 68 ampulla of Vater cases, were included in this study. In addition, 1,037 patients with biliary stones (774 gallbladder stones and 263 bile duct stones) without a history of cancer were selected from the same hospital as the index cancer cases and were frequency-matched to the index cancer cases on age (5-year groups) and gender. A total of 959 subjects who were permanent residents of Shanghai and had no history of any type of cancer were randomly selected from the Shanghai Resident Registry (~6 million residents) as population controls. Controls were frequency-matched to cancer cases in a 1-to-1 ratio based on the age (5-year groups) and gender distributions of biliary tract cancer cases. All study subjects provided written informed consent. The Institutional Review Boards of the National Cancer Institute and Shanghai Cancer Institute approved the study protocol.

Clinical and pathologic review

Diagnoses of all biliary tract cancer cases were confirmed by a panel of clinicians, ultrasonographers and pathologists, using a combination of medical and surgical records, pathology slides and radiological films. Because of the late-stage diagnosis of most biliary tract cancers, pathology materials were available to confirm only 70% of the cancer cases. Among cases without pathology materials, we reviewed imaging data, medical records and surgical reports to confirm the diagnosis of cancer on clinical grounds. As part of the diagnostic workup, all cancer cases underwent magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP) or computed tomography (CT). All bili-

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any stone cases were confirmed clinically by review of abdominal ultrasound data or ERCP films, or pathologically for those who underwent cholecystectomy.

Data collection

Study subjects were interviewed by trained interviewers, using a structured questionnaire to obtain information on demographic characteristics, medical and occupational histories, lifestyle behaviors and diet. Information was collected on tea drinking, including age of first use, duration of consumption (years) and monthly intake (weight of tea leaves in grams). Ever tea drinkers were defined as subjects who consumed at least one cup of tea per day for more than 6 months. Current drinkers were a subset of ever tea drinkers who consumed tea at the time of interview. Lifetime tea consumption was calculated as monthly intake (grams) multiplied by 12 (months) and duration of consumption (years). The response rate for the interview was over 95% among cases and 85% among controls. All interviews were recorded and reviewed to ensure adherence to the study protocol. Five percent of the subjects were randomly re-interviewed within 3 months of the first interview to assess reproducibility. Concordance between the 2 interviews on responses to key questions was greater than 90%.

Assessment of gallstones

Gallstone status among cancer cases was assessed by both self-reported history and clinical data from MRI, ERCP and CT tests. Among population controls, gallstone status was assessed by self-reported history and by abdominal ultrasound among those who gave consent for the procedure (85% of all population controls).

Statistical analysis

Associations of tea consumption with biliary tract cancers and biliary stones were assessed by calculating odds ratios (ORs) and 95% confidence intervals (CIs), using unconditional logistic regression. To make the appropriate case-control comparisons, only those controls at risk of developing each disease outcome were considered. Specifically, controls without a history of cholecystectomy were compared with gallbladder cancer cases, whereas controls without biliary stones were compared with biliary stone cases, and all population controls were compared with bile duct and ampulla of Vater cancer cases.

The Fisher's exact test was used to detect differences between cases and controls for selected characteristics. Those characteristics with statistically significant differences ($p < 0.05$) were considered potential confounders for biliary tract cancers or stones, and their associations with tea drinking were subsequently evaluated. Factors associated with both tea drinking and biliary tract cancer or stones were adjusted for in the logistic regression models.

The risk estimates for gallbladder cancer, bile duct cancer and biliary stones (gallstones and bile duct stones combined) were evaluated by tea drinking status (never, ever or current tea drinker). The risk of ampulla of Vater cancer associated with tea drinking was not estimated due to the small number of cases ($n = 68$). Among ever tea drinkers, biliary tract cancer and stone risks were assessed further by age of first tea consumption (years), duration of tea consumption (years), monthly tea intake (grams) and lifetime tea consumption (grams). Median values for these tea drinking characteristics were determined among population controls and were used as categorical cutoffs for risk estimate calculations. Gender-specific risk estimates were calculated, because median values of tea drinking characteristics differed substantially between men and women. Initially, a full model was fit that included all potential confounding variables: age at interview, education, body mass index [BMI, weight (kg)/height (m)²], smoking, alcohol use, hypertension, diabetes, allium vegetable intake, family history of gallstones and gallstone status (for cancer cases only). We subsequently fitted a parsimonious model including only the variables associated with both tea consumption and biliary disease, *i.e.*, age at interview, education and BMI (for biliary

stone cases only). Tests of linear trend were conducted categorically for all tea drinking characteristics, including age of first use, duration, monthly intake and lifetime consumption.

Results

The frequency distributions of selected characteristics among cases and controls are shown in Table I. The majority of gallbladder cancers (73.1%) and biliary stones (62.4%) occurred among women, whereas slightly more cancers of the bile duct (51.8%) and ampulla of Vater (54.4%) occurred among men. The prevalence of gallstones was significantly higher among cancer cases at all three subsites than controls. Gallbladder cancer and biliary stone cases had a significantly higher prevalence of diabetes and obesity (BMI ≥ 25 kg/m², cutoff for obesity suggested for Asians),¹⁹ but a lower prevalence of alcohol consumption. Bile duct cancer, ampulla of Vater cancer and biliary stone cases were less likely than controls to have hypertension. Ampulla of Vater cancer and biliary stone cases had significantly greater intake of preserved foods. There was no difference in allium vegetable or total caloric intake between cases and controls, except for gallbladder cancer cases who consumed significantly fewer calories per day compared with controls.

Among the 959 controls, 394 (41%) were ever tea drinkers who consumed at least 1 cup of tea per day for at least 6 months. Most ever tea drinkers were also current tea drinkers at the time of interview, with 363 (92%) of the 394 ever tea drinkers being current tea drinkers. Ninety-two percent of the ever tea drinkers reported drinking green tea, the most commonly consumed type of tea in China.²⁰ Since risk estimates for current and ever tea drinkers were similar, in Table II, we present the risk of biliary tract cancers and stones in relation with tea consumption among ever tea drinkers by gender. Compared to women, men started drinking tea at an earlier age (median: 30 vs. 35 years), drank for a longer duration (median: 30 vs. 20 years), consumed a greater quantity (median: 250 vs. 150 g/month) and had a higher lifetime consumption (median: 81,600 vs. 24,600 g).

Among women, tea drinking was associated with lower risks of gallbladder and bile duct cancers and of biliary stones. Female ever tea drinkers had a 44%, 35% and 27% reduced risk of gallbladder cancer (OR = 0.56; 95% CI = 0.38–0.83), bile duct cancer (OR = 0.65; 95% CI = 0.37–1.14) and biliary stones (OR = 0.73; 95% CI = 0.54–0.98), respectively. In addition, several tea drinking characteristics, including age of first use, duration, monthly intake and lifetime consumption were also significantly and inversely associated with gallbladder cancer risk. Among women, the protective effect of tea on biliary tract cancer persisted after further adjustment for gallstones and other covariates.

Among men, risk estimates for biliary tract cancers and stones associated with tea drinking were generally below 1.0, but were not statistically significant. Smoking and tea drinking were strongly correlated among Chinese men (r_{Spearman} for tea and smoking = 0.23, $p < 0.0001$). Further adjustment for smoking did not change the risk estimates of biliary tract cancers or stones among men. However, when the effect of tea drinking was evaluated by smoking status, the non-significant protective effect was evident among male nonsmokers, but not male smokers, in particular for bile duct cancer (nonsmokers: OR = 0.63; 95% CI = 0.28–1.43; smokers: OR = 1.17; 95% CI = 0.63–2.19). Because of the small number of male nonsmokers, we had limited power to detect a significant interaction between smoking and tea drinking among men (interaction p for bile duct cancer = 0.25).

Discussion

In this population-based study, tea drinking was associated with reduced risks of gallbladder and bile duct cancers, as well as biliary stones, especially among women. These findings add to the accumulating epidemiologic evidence linking tea consumption

TABLE 1 – SELECTED CHARACTERISTICS OF SUBJECTS BY CASE-CONTROL STATUS

	Population controls		Gallbladder cancer ¹		Bile duct cancer ²		Ampulla of Vater cancer ²		Biliary stones ³	
	N	%	N	%	N	%	N	%	N	%
Total	959	100.0	368	100.0	191	100.0	68	100.0	1,037	100.0
Gender										
Male	373	38.9	99	26.9*	99	51.8*	37	54.4*	390	37.6*
Female	586	61.1	269	73.1	92	48.2	31	45.6	647	62.4
Age (years)										
<50	71	7.4	29	7.9	18	9.4	4	5.9	200	19.3*
50–59	151	15.7	48	13.0	30	15.7	8	11.8	222	21.4
60–69	452	47.1	174	47.3	96	50.3	34	50.0	424	40.9
≥70	285	29.7	117	31.8	47	24.6	22	32.3	191	18.4
Education										
Illiterate and elementary	396	41.3	198	53.8*	86	45.0	29	42.6	317	30.6*
High school	423	44.1	129	35.1	74	38.8	31	45.6	537	51.8
College and above	140	14.6	41	11.1	31	16.2	8	11.8	183	17.6
Marital status										
Married	751	78.3	284	77.2	161	84.3	55	80.9	884	85.3*
Widowed	175	18.2	77	20.9	27	14.1	12	17.6	134	12.9
Divorced, separated	33	3.4	7	1.9	3	1.6	1	1.5	19	1.8
Ever drink tea										
No	565	58.9	267	72.6*	110	57.6	39	57.4	625	60.3
Yes	394	41.1	101	27.4	81	42.4	29	42.6	412	39.7
Ever drink alcohol										
No	760	79.2	316	85.9*	141	73.8	53	77.9	870	83.9*
Yes	198	20.6	52	14.1	50	26.2	15	22.1	167	16.1
Ever smoke										
No	674	70.3	279	75.8*	115	60.2*	38	55.9*	754	72.7
Yes	285	29.7	89	24.2	76	39.8	30	44.1	283	27.3
Body mass index ⁴ (kg/m ²)										
<23.0	484	50.5	150	40.8*	96	50.3	30	44.1	396	38.2*
23.0–24.9	197	20.5	73	19.8	49	25.7	15	22.1	259	25.0
≥25.0	278	29.0	145	39.4	46	24.1	23	33.8	382	36.8
Biliary stones										
No	735	76.6	60	16.3*	64	33.5*	32	47.1*	0	0.0
Yes	224	23.4	308	83.7	127	66.5	36	52.9	1,037	100.0
Hypertension										
No	553	57.7	230	62.5	130	68.1*	48	70.6*	695	67.0*
Yes	406	42.3	138	37.5	61	31.9	20	29.4	342	33.0
Diabetes										
No	881	91.9	316	85.9*	171	89.5	63	92.6	926	89.3*
Yes	78	8.1	52	14.1	20	10.5	5	7.4	111	10.7
Preserved food (g/month)										
Quartile 1 (<195.0)	259	27.0	89	24.2	41	21.5	15	22.1*	239	23.1*
Quartile 2 (195.0–426.5)	241	25.1	93	25.3	43	22.5	15	22.1	201	19.4
Quartile 3 (426.6–917.1)	244	25.4	96	26.1	52	27.2	11	16.2	271	26.1
Quartile 4 (>917.1)	215	22.4	90	24.4	55	28.8	27	39.7	326	31.4
Allium Vegetable (g/month)										
Quartile 1 (<165.5)	272	28.4	119	32.3	63	33.0	22	32.4	312	30.1
Quartile 2 (165.5–330.4)	267	27.8	109	29.6	43	22.5	21	30.9	292	28.1
Quartile 3 (330.5–706.0)	249	26.0	97	26.4	52	27.2	13	19.1	228	22.0
Quartile 4 (>706.0)	171	17.8	43	11.7	33	17.3	12	17.6	205	19.8
Total Calories (kcal/day)										
Quartile 1 (<1834)	239	24.9	113	30.7*	47	24.6	16	23.5	242	23.3
Quartile 2 (1834–2220)	242	25.2	109	29.6	47	24.6	12	17.6	244	23.5
Quartile 3 (2221–2698)	258	26.9	76	20.7	49	25.7	23	33.8	249	24.0
Quartile 4 (>2698)	220	22.9	70	19.0	48	25.1	17	25.0	302	29.1

¹Compared with population controls without cholecystectomy. ²Compared with population controls. ³Compared with population controls without biliary stones. ⁴Cutpoints for overweight and obesity among Asians. * $p < 0.05$ for Fisher's exact test for difference between cases and controls.

with a lower risk of various cancers, particularly of the digestive tract.

The exact mechanisms by which tea can protect against biliary tract cancer are unclear, but may involve antiproliferative and anti-inflammatory properties of tea polyphenols, in particular epigallocatechin-3-gallate (EGCG).²¹ Laboratory studies have shown that EGCG can inhibit inflammatory processes that are involved in the pathogenesis of epithelial cancers.^{22–24} Specifically, it has been shown that EGCG can inhibit (i) the expression of cyclooxygenase-2 (COX-2),^{25,26} a pro-inflammatory mediator, that has been shown to be overexpressed in biliary tract cancer tissue;^{27–29} (ii) the expression of other key inflammatory mediators, such as

cytokines and tumor necrosis factor- α ;^{22–24} and (iii) tumor growth through modulation of regulatory enzymes, such as cyclin-dependent kinases.³⁰ Data specific to biliary tissue are limited, but a laboratory study of biliary tract carcinoma showed that EGCG can suppress cell growth and the invasive ability of the carcinoma cells.¹⁰

Despite the longer duration and higher quantity of tea consumption among men, the statistically significant inverse relationship between tea drinking and risk of biliary tract cancers and stones was largely limited to women. Previous studies of other gastrointestinal cancers conducted in Asia have also reported a stronger protective effect of tea drinking in women than in men.^{4,6,31–34}

TABLE II – ODDS RATIOS AND 95% CONFIDENCE INTERVALS FOR BILIARY TRACT CANCERS AND STONES IN RELATION TO TEA DRINKING BY GENDER

	Gallbladder cancer			Bile duct cancer			Biliary Stones		
	Cases/controls	OR ¹	95% CI	Cases/controls	OR ¹	95% CI	Cases/controls	OR ²	95% CI
Male									
Tea drinking status									
Never	39/126	1.00	–	35/133	1.00	–	130/110	1.00	–
Ever ³	60/231	0.82	0.52–1.30	64/240	1.03	0.64–1.64	260/203	0.98	0.70–1.35
Age started drinking (years)									
<30	36/101	1.12	0.66–1.91	38/104	1.42	0.84–2.42	137/85	1.16	0.79–1.70
≥30	24/130	0.59	0.33–1.04	26/136	0.73	0.42–1.29	123/118	0.84	0.58–1.22
			<i>p</i> _{trend} = 0.75			<i>p</i> _{trend} = 0.22			<i>p</i> _{trend} = 0.50
Duration of drinking (years)									
<30	23/113	0.63	0.35–1.14	28/114	0.90	0.51–1.59	134/105	0.86	0.59–1.26
≥30	37/118	0.99	0.59–1.69	36/126	1.15	0.67–1.96	126/98	1.11	0.76–1.64
			<i>p</i> _{trend} = 0.92			<i>p</i> _{trend} = 0.63			<i>p</i> _{trend} = 0.65
Monthly intake (grams)									
<250	29/91	1.01	0.58–1.76	24/94	0.99	0.56–1.79	134/81	1.33	0.90–1.97
≥250	28/140	0.63	0.37–1.09	40/146	1.04	0.62–1.75	126/122	0.75	0.52–1.09
			<i>p</i> _{trend} = 0.10			<i>p</i> _{trend} = 0.87			<i>p</i> _{trend} = 0.13
Lifetime consumption (grams) ⁴									
<81,600	29/116	0.79	0.46–1.37	30/119	0.96	0.56–1.67	151/107	1.05	0.72–1.51
≥81,600	28/115	0.77	0.44–1.33	34/121	1.09	0.64–1.86	109/96	0.89	0.61–1.32
			<i>p</i> _{trend} = 0.33			<i>p</i> _{trend} = 0.76			<i>p</i> _{trend} = 0.59
Female									
Tea drinking status									
Never	228/402	1.00	–	75/432	1.00	–	495/311	1.00	–
Ever ³	41/143	0.56	0.38–0.83	17/154	0.65	0.37–1.14	152/111	0.73	0.54–0.98
Age started drinking (years)									
<35	18/66	0.55	0.32–0.95	3/68	0.26	0.08–0.85	87/51	0.87	0.59–1.30
≥35	23/77	0.57	0.35–0.94	14/86	0.94	0.51–1.75	65/60	0.61	0.41–0.90
			<i>p</i> _{trend} = 0.01			<i>p</i> _{trend} = 0.04			<i>p</i> _{trend} = 0.15
Duration of drinking (years)									
<20	19/63	0.58	0.33–0.99	11/69	0.93	0.47–1.86	75/46	0.76	0.50–1.16
≥20	22/80	0.55	0.33–0.91	6/85	0.41	0.17–0.98	77/65	0.70	0.48–1.02
			<i>p</i> _{trend} = 0.01			<i>p</i> _{trend} = 0.06			<i>p</i> _{trend} = 0.04
Monthly intake (grams)									
<150	20/81	0.51	0.33–0.86	7/86	0.48	0.21–1.08	77/65	0.60	0.41–0.88
≥150	21/60	0.64	0.38–1.08	10/66	0.88	0.43–1.78	72/44	0.91	0.60–1.38
			<i>p</i> _{trend} = 0.01			<i>p</i> _{trend} = 0.32			<i>p</i> _{trend} = 0.17
Lifetime consumption (grams) ⁴									
<24,600	19/72	0.52	0.30–0.89	7/76	0.54	0.24–1.22	69/56	0.62	0.42–0.94
≥24,600	22/69	0.62	0.37–1.03	10/76	0.77	0.38–1.55	80/53	0.83	0.56–1.23
			<i>p</i> _{trend} = 0.01			<i>p</i> _{trend} = 0.24			<i>p</i> _{trend} = 0.12

¹Odds ratios for gallbladder and bile duct cancer were adjusted for age at interview and education status.—²Odds ratios for biliary stones were adjusted for age at interview, education, and body mass index.—³Drink at least 1 cup of tea per day for 6 months.—⁴Lifetime consumption = monthly intake (g) × 12 (months) × duration of drinking (years).

The less evident effect of tea drinking on biliary tract cancer in men may be related in part to the strong correlation between tea drinking and cigarette smoking among Chinese men, making it difficult to assess an independent effect of tea drinking. Among controls, 62% of men *v.s.* 9% of women were ever smokers. Among male tea drinkers, 70% smoked (r_{Spearman} for tea and smoking = 0.23, $p < 0.0001$), whereas only 12% of the women who drank tea also smoked (r_{Spearman} = 0.06, $p = 0.18$). In addition, among men, smokers consumed more tea than nonsmokers (median lifetime tea consumption: smokers 91,200 g, nonsmokers 60,000 g) and heavy smokers were also heavy tea drinkers. In our study, smoking was not associated with an increased risk of gallbladder or ampulla of Vater cancers, but was associated with a 37% nonsignificant increased risk of bile duct cancer among men. Results from previous studies were mixed, with two reporting positive associations between smoking and bile duct cancer.^{35,36} Hence, we cannot rule out the possibility that smoking may be related to bile duct cancer, and thus may attenuate the protective effects of tea drinking among men. The fact that the protective effect of tea drinking was evident among male nonsmokers and not male smokers further suggests a complex interplay of tea drinking and smoking for bile duct cancer among men. However, because there are few nonsmoking men in this population, the interaction between tea drinking and smoking on the risk of biliary tract cancer was not statistically significant.

Another possible explanation for the significant protective effect of tea drinking in women may be related to the effects of EGCG on estrogen biosynthesis and other hormonal processes. Obesity and parity have been linked consistently to higher risks of gallstones^{16,37} and gallbladder cancer,^{16,38} probably due to higher levels of circulating estrogens among obese women and during pregnancy.^{39–41} Both animal and human data suggest that tea polyphenols, in particular EGCG, can affect estrogen metabolism, although the precise mechanisms are unclear.^{41–44} In humans, a recent cross-sectional study showed that women who drank tea had lower levels of circulating estrogens than nondrinkers.⁴¹ In laboratory studies, it has been shown that EGCG inhibits the methylation of catechol estrogens in the human liver by catechol-*O*-methyltransferase⁴⁴ and binds to estrogen receptors (ER- α and ER- β), thereby influencing ER-mediated gene expression to exert an antiestrogenic effect.^{42,43} In animal studies, tea catechins reduce serum levels of testosterone, leptin, insulin and insulin-like growth factor-1,⁴⁵ which may also play a role in the development of gallbladder cancer and/or gallstones.

Several strengths and limitations of our study should be noted. Given the high case ascertainment (>95%) and response rates (>80%), selection and survival biases were minimal. Also, rigorous pathology and clinical review minimized misclassification of outcome and gallstone status. Any misclassification of tea drinking characteristics, such as amount and duration, due to the diffi-

culty in recall, is likely to be nondifferential between cases and controls. Despite the relatively large size of our study, there was limited statistical power to accurately evaluate risks of bile duct and ampullary cancers associated with tea drinking, and to formally test for interactions among covariates. Although we cannot rule out the possibility that our findings resulted from chance, given the abundant animal and laboratory data on tea drinking and our consistent findings for lower risks of cancers of the gallbladder and bile duct and biliary stones, it is likely that tea drinking can reduce the risk of biliary tract diseases, at least among nonsmoking women.

In summary, this population-based case-control study in Shanghai, China, revealed a protective effect of tea consumption on biliary

tract cancer and biliary stones among women. Future studies are needed to replicate these results in other populations and clarify the hormonal and other mechanisms that may be involved.

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